

HED Document No. 013434

DATE: June 10, 1999

MEMORANDUM

SUBJECT: *DICHLORVOS (DDVP)* - **REPLACEMENT OF HUMAN STUDY USED IN RISK ASSESSMENTS** - Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Pauline Wagner, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Sue Hummel, Branch Senior Scientist
Reregistration Branch 4
Health Effects Division (7509C)

PC Code: 084001

On February 18, 1999, the Health Effect Division's (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the toxicology database for dichlorvos and selected doses and toxicology endpoints for risk assessment, based solely on **animal toxicity studies**. The HIARC also determined the appropriate uncertainty factors and margins of exposures for dietary and non-dietary risk assessments. **For clarity, transparency, and utility, the decisions made at the previous HIARC meetings along with those made at this meeting are presented in this report. Consequently, the information contained in this report should be used for risk assessments and supersedes all other reports (RfD, TES, HIARC, etc) for dichlorvos.**

Committee Members in Attendance

Members present were: David Anderson, William Burnam, Virginia Dobozy, Pam Hurley, Mike Ioannou, Tina Levine, Susan Makris, Nicole Paquette, Kathleen Raffaele, Jess Rowland, PV Shah, Brenda Tarplee (Executive Secretary), and Pauline Wagner. Member in absentia: Karen Hamernik.

Other HED staff present at the meeting were: George Ghali, Ray Kent, and Abdallah Khasawinah.

Brenda Tarplee
Executive Secretary
Hazard Identification Assessment Review Committee

I. BACKGROUND

The Health Effects Division's Hazard Identification Assessment Review Committee selected doses and endpoints for dichlorvos for acute and chronic dietary as well as occupational exposure risk assessments. (HIARC Report dated 12/19/97; HED Document No. 012448). On May 7, 1998, the HIARC reviewed the pathology Work Group's analyses of the acute and subchronic studies in hens as well as a prenatal developmental toxicity study in guinea pigs reported in the open literature (HIARC Report dated June 3, 1998, HED Document No. 012629).

In December 10-11, 1998, the Science Advisory Board/Scientific Advisory Panel discussed both the ethical concerns and the scientific merit of using humans subjects for testing pesticides. The Agency is currently developing a policy for the use of human studies in risk assessment. In the interim, HED has taken the following course of action.

In January, 1999, the HIARC developed a specific outline of parameters and questions for the re-examination of human studies. Human studies were used in endpoint selection for risk assessment for eight organophosphates, including dichlorvos. These studies were re-evaluated according to the parameters and questions developed by the Committee. The HIARC then selected doses and endpoints from toxicity studies with animals for each of these eight organophosphate. The HIARC examined the human data in conjunction with the animal data to determine the appropriate inter-species uncertainty factor.

In the evaluation of the comparative toxicology data in laboratory animals and humans, when the data was suitable for comparison, the Committee relied mainly on the LOAEL for cholinesterase inhibition at comparable time points (duration). The comparative data were evaluated as follows:

If the comparative data indicate (by the dose level and the magnitude of the effect) that humans are more sensitive than laboratory animals, there is no justification for reducing the 10x inter-species uncertainty factor.

If the comparative data indicate (by the dose level and the magnitude of the effect) that humans and laboratory animals are equally sensitive or that humans are less sensitive than laboratory animals, consideration was given to reducing the inter-species uncertainty factor.

On January 14, 1999, the HIARC evaluated the studies conducted in human volunteers (Gledhil, 1977; MRID No. 44317901 and 44248802) with dichlorvos using the parameters developed for evaluation of the human studies. The HIARC classified both the studies as *supplemental* because the results of these studies provided useful scientific information that can be used as supportive data along with the results from the animal studies, but the studies alone are not sufficient for endpoint selection or risk assessments due to technical limitations.

On February 18, 1999, the HIARC evaluated the doses and toxicology endpoints selected for DDVP based solely on animal toxicity studies. The HIARC also determined the appropriate uncertainty factors and margins of exposure for dietary and non-dietary risk assessments.

For clarity, transparency, and utility, the decisions made at the previous HIARC meetings along with those made at this meeting are presented in this report. Consequently, the information contained in this report should be used for risk assessments.

II. HAZARD IDENTIFICATION

A. Acute Dietary Reference Dose (RfD)

Study: Acute Neurotoxicity -Rat §81-82

MRID No. 42655301

Executive Summary: In an acute neurotoxicity study, Sprague Dawley rats (12/sex/dose) received a single oral dose of dichlorvos (97.8%) at doses of 0, 0.5, 35 or 70 mg/kg. Behavioral Testing (Functional Observation Battery, FOB, and Motor Activity) was conducted pretest, 15 minutes after treatment, and on study days 7 and 14. Cholinesterase measurements were NOT performed. The NOAEL was 0.5 mg/kg and the LOAEL was 35 mg/kg based on alterations in FOB (gait changes, whole body tremors, clonic convulsions, reduced heat or absent forelimb/hind limb grasp, constricted pupils and exophthalmus), decreased motor activity, catalepsy and reduction in body temperature.

Dose and Endpoint for Risk Assessment: NOAEL=0.5 mg/kg based on alterations in FOB at 35 mg/kg (LOAEL).

Uncertainty Factor: 300 (10x for inter-species variation, 10x for intra-species extrapolation, and 3x for the lack of cholinesterase measurement).

$$\text{Acute RfD} = \frac{0.5 \text{ mg/kg/day (NOAEL)}}{300 \text{ (UF)}} = 0.002 \text{ mg/kg}$$

Comments about study, endpoint and UF: **This dose and endpoint replaces the previous dose/endpoint based on the human study.** The dose/endpoint/study is appropriate for this risk assessment because the effects were seen after a single exposure. The UF includes the 10x for inter-species extrapolation, 10x for intra-species variation, and a 3x since cholinesterase activity was not measured in this study. The HIARC concluded that the 10x inter-species extrapolation factor cannot be modified/alterd. The human study (Gledhil, 1997) is determined to be useful only as

supplemental data. Although this study provided some supportive scientific data, it is not appropriate for use in risk assessment since only red blood cell (not plasma) cholinesterase activity was measured. The lack of comparable endpoints for acute effects between the human (red blood cell cholinesterase data) and animal (no cholinesterase measurement) studies make relative sensitivity difficult to determine. Although there was no effect on RBC cholinesterase activity in the human study following a single 0.5 mg/kg dose, this effect cannot be compared to the results of the animal study since RBC cholinesterase activity was not measured. This dose was the NOAEL after a single dose in the animal study, but cholinesterase activity was not measured. In addition, a statistically significant decrease in RBC cholinesterase activity was seen in humans following a single exposure to dichlorvos at 1 mg/kg.

B. Chronic Dietary RfD

Study: Chronic Toxicity-Dog

§83-1b

MRID No. 41593101

Executive Summary: In a chronic feeding study, groups of beagle dogs were administered dichlorvos by capsule for 52 weeks at dose levels of 0, 0.1, 1.0 and 3.0 mg/kg/day. The 0.1 mg/kg/day dose was lowered to 0.05 mg/kg/day on day 22 due to the inhibition of plasma cholinesterase noted after 12 days. Plasma cholinesterase was decreased in males (21.1%) and females (25.7%) at week 2 in the 0.1 mg/kg/day group which was then reduced to 0.05 mg/kg/day. Time points after week 2, plasma cholinesterase activity was only significantly reduced in males (39.1 to 59.2%) and females (41.0 to 56.7%) in the mid-dose group and in males (65.1 to 74.3%) and females (61.1 to 74.2%) in the high dose group at all other later time intervals. Although RBC cholinesterase activity was reduced in males (23.6%) and females (50.1%) at week 6 in the low-dose group, this was believed to be residual effect on RBC cholinesterase of the higher dose of 0.1 mg/kg/day. Much lower levels were observed in this group after week 6. At time points after week 6, RBC cholinesterase activity was only significantly decreased in males (43.0 to 53.9) and females (38.0 to 51.9) in the mid-dose group and in males (81.2 to 86.9%) and females 79.2 to 82.5%) in the high-dose groups. Brain cholinesterase activity was significantly reduced in males (22%) in the mid-dose group and in males (47%) and females (29%) in the high dose group. The NOAEL was 0.05 mg/kg/day and the LOAEL was 0.1 mg/kg/day based on plasma and RBC cholinesterase inhibition in males and females and brain cholinesterase inhibition in males.

Dose and Endpoint for Risk Assessment: NOAEL=0.05 mg/kg based on plasma and RBC cholinesterase inhibition in males and females and brain cholinesterase inhibition in males

observed at 0.1 mg/kg/day (LOAEL).

Uncertainty Factor: 100 (10x for inter-species variation and 10x for intra-species extrapolation).

$$\text{Chronic RfD} = \frac{0.05 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.0005 \text{ mg/kg/day}$$

Comments about study, endpoint and UF **No change from the previous dose/endpoint selected based on the dog study cited above (i.e., human data was not used previously).** As stated in the 12/19/97 HIARC report, the Committee did not use the human data since the treatment regimen in that study is not adequate to characterize lifetime exposure, did not include plasma cholinesterase measurement, and cholinesterase inhibition did not demonstrate a steady state (equilibrium) by the end of the study at three weeks, i. e. the inhibition of cholinesterase was progressive in this case and NOAEL was not achieved.

C. Occupational/Residential Exposure

1. Dermal Absorption

An acceptable dermal absorption study (MRID No. 41435201) demonstrated 11% dermal absorption 10 hours after exposure.

Dermal Absorption Factor: 11%

2. Short-Term Dermal (1-7 days)

Study Selected: Developmental - Rabbit §83-3b

MRID No. 41802401

Executive Summary: Groups of New Zealand White rabbits (16/dose) received oral administration of dichlorvos (97%) in distilled water at dose levels of 0, 0.1, 2.5 or 7.0 mg/kg/day during gestation days 7 through 19, inclusive. For Maternal Toxicity, the NOAEL was 0.1 mg/kg/day and the LOAEL was 2.5 mg/kg/day based on cholinergic signs and decreases in body weight and body weight gain. For Developmental Toxicity, the NOAEL was > 7 mg/kg/day (highest dose tested) a LOAEL was not achieved.

Dose and Endpoint for Risk Assessment: Maternal NOAEL = 0.1 mg/kg/day based on the cholinergic signs and decreases in body weight at 2.5 mg/kg/day.

Comments about Study and Endpoint: **This dose and endpoint replaces the previous dose/endpoint based on the human study.** The HIARC determined

that the human study (Gledhil, 1997) is useful only as *supplemental* data. Although this study provided some supportive scientific data, it is not appropriate for use in risk assessment since only red blood cell (not plasma) cholinesterase activity was measured. In addition, the magnitude of the effect following administration of a low dose to humans (RBC cholinesterase inhibition of approximately 30% following administration of 0.3 mg/kg for 12 to 14 days) was similar to inhibition following administration of a higher dose to rats for a longer duration (RBC cholinesterase inhibition of approximately 25% following administration of 1.5 mg/kg for 7 weeks). These data indicate that humans may be more sensitive than animals to dichlorvos exposure. Since an oral value was selected, 11% dermal absorption factor should be used for route-to-route extrapolation in dermal risk assessments.

This risk assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study: Chronic Toxicity-Dog

§83-1b

MRID No. 41593101

Executive Summary: See Chronic Dietary

Dose and Endpoint for Risk Assessment: NOAEL 0.05 mg/kg/day based on inhibition of plasma and red blood cell cholinesterase activity at 1 mg/kg/day at the 13 week measurement.

Comments about Study and Endpoint: **This dose and endpoint replaces the previous dose/endpoint based on the human study.** The HIARC determined that the human study (Gledhil, 1997) is useful only as *supplemental* data. Although this study provided some supportive scientific data, it is not appropriate for use in risk assessment since only red blood cell (not plasma) cholinesterase activity was measured. In addition, the magnitude of the effect following administration of a low dose to humans (RBC cholinesterase inhibition of approximately 30% following administration of 0.3 mg/kg for 12 to 14 days) was similar to inhibition following administration of a higher dose to rats for a longer duration (RBC cholinesterase inhibition of approximately 25% following administration of 1.5 mg/kg for 7 weeks). These data indicate that humans may be more sensitive than animals to dichlorvos exposure.

This dose/endpoint is appropriate for this exposure period since the effects were seen at the 13 week measurement. Since an oral value was selected, 11% dermal absorption factor should be used for route-to-route extrapolation in dermal risk

assessments.

This risk assessment is required.

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: None

MRID No. None

Executive Summary: None

Dose/Endpoint for Risk Assessment: The use pattern of dichlorvos does not indicate a concern for long-term dermal exposure, therefore, a dose/endpoint was not identified.

This risk assessment is NOT required at the present time.

5. Short-Term Inhalation (1-7 Days)

Study Selected: Developmental - Rabbit §83-3b

MRID No. 41802401

Executive Summary: See Short-Term Dermal

Dose and Endpoint for Risk Assessment: Maternal (oral) NOAEL = 0.1 mg/kg/day based on the cholinergic signs and decreases in body weight at 2.5 mg/kg/day (LOAEL).

Comments about Study and Endpoint: **This dose and endpoint replaces the previous dose/endpoint based on the human study.** The rationale for not using the human study is provided under Short-Term Dermal.

Since an oral value was selected 100% inhalation absorption factor should be used for route-to-route extrapolation in inhalation risk assessments.

This risk assessment is required.

6. Intermediate-Term Inhalation (7 Days to Several Months)

Study: Chronic Toxicity-Dog §83-1b

MRID No. 41593101

Executive Summary: See Chronic Dietary

Dose and Endpoint for Risk Assessment: Oral NOAEL 0.05 mg/kg/day based on inhibition of plasma and red blood cell cholinesterase activity at 1 mg/kg/day at the 13 week measurement.

Comments about Study and Endpoint: **This dose and endpoint replaces the previous dose/endpoint based on the human study.** The rationale for not using the human study is provided under Short-Term Dermal.

Since an oral value was selected, 100% inhalation absorption factor should be used for route-to-route extrapolation in inhalation risk assessments.

7. Long-Term Inhalation (Several Months to Life Time)

Study: Inhalation Carcinogenicity - Rat §83-2a

MRID No. 0057695 & 00632569

Executive Summary: Groups of 50/sex/group Carworth rats were exposed to atmospheres containing dichlorvos vapor for 23 hours/day, 7 days/week at concentrations of 0, 0.05, 0.5, and 5 mg/m³ equivalent to 0.055, 0.5, and 5.0 mg/kg/day for 2 years. Animals were observed for clinical signs of toxicity, hematology, clinical chemistry and plasma and RBC cholinesterase activity. Brain cholinesterase activity was monitored at study termination. There were no toxic signs, and no organ weight or organ to body weight changes, or hematological changes attributable to administration of DDVP. Body weights were significantly decreased in mid and high dose males up to study termination, and in high dose females throughout the study. Plasma, RBC, and brain cholinesterase activity were significantly reduced in the mid and high dose groups (76, 72, and 90 and 83, 68, and 90 percent of control in mid dose males and females, and to 38, 4, and 21, and 22, 5, and 16 percent of control in the high dose male and female groups, respectively). RBC cholinesterase activity was reduced to 88 percent of control in the low dose females. The NOEL for cholinesterase inhibition was 0.00005 mg/L and the LOAEL was 0.0005 mg/L.

Dose and Endpoint for Risk Assessment: NOAEL = 0.00005 mg/L based on plasma, RBC and brain cholinesterase inhibition observed at the next higher dose level of 0.0005 mg/L (LOAEL).

Comments about Study and Endpoint: This dose/endpoint/study is appropriate for this exposure route and period of concern, and has been used to derive the Reference Concentration (RfC) by the Agency RfD/RfC Work Group.

D. Margin of Exposure for Occupational/Residential Exposures

The HIARC determined that a Margin of Exposure (MOE) of **100 is adequate for occupational exposure risks.**

The FQPA Safety Factor Committee has determined that a 3x FQPA safety factor is required for dichlorvos (See the FQPA Safety Factor Committee Report dated August 6, 1998). Therefore, for a **MOE of 300 is required for residential exposure risks.**

E. Aggregate Exposure (Food + Water + Residential) Risk Assessments

For **acute** aggregate exposure risk assessment, combine the **high end** exposure values from food plus water and compare it to the **acute RfD**.

For **chronic** aggregate exposure risk assessment, combine the **average end** exposure values from food plus water and compare it to the **chronic RfD**.

For **short and intermediate-term** aggregate exposure risk assessment, dermal and inhalation exposure should be converted to oral equivalent doses (i.e., corrected for % dermal and inhalation absorption since oral values were selected). The oral equivalent doses should be added to the average from food plus water, as well as incidental oral exposure, and compared to the oral NOAELs to calculate aggregate risk MOEs. The MOEs **can NOT be combined** due to lack of common toxicology endpoint via these routes.

For **long-term-term** aggregate exposure risk assessment, combine the average exposure values from food plus water to the dermal and inhalation exposures (converted to oral equivalents). The MOEs derived for the oral and inhalation exposures may be combined to obtain a total MOE due to the common toxicity endpoint (cholinesterase inhibition) observed via the chronic oral and inhalation routes of exposures.

$$MOE_{Total} = \frac{1}{\frac{1}{MOE_{Oral}} + \frac{1}{MOE_{Inhalation}}}$$

III. FQPA ASSESSMENT

The FQPA Safety Factor Committee met on June 15 and 16, 1998 to evaluate the hazard and

exposure data for DDVP and recommend application of the FQPA Safety Factor (as required by Food Quality Protection Act of August 3, 1996), to ensure the protection of infants and children from exposure to these pesticides.

The FQPA Safety Factor Committee has determined that a 3x FQPA safety factor is required for the protection of infants and children from dietary and residential exposure to dichlorvos. For details, refer to the FQPA Safety Committee Report dated August 6, 1998.

IV. ACUTE TOXICITY

Guideline No.	Study Type	MRID No.	Results	Toxicity Category
81-1	Acute Oral-	0005467	LD ₅₀ = 80 mg/kg (M); 56 mg/kg (F)	II
81-2	Acute Dermal	0005467	LD ₅₀ = 107 mg/kg (M); 75 mg/kg (F)	I
81-3	Acute Inhalation	00137239	LC ₅₀ = > 0.218 mg/L	
81-4	Primary Eye Irritation	258738	Mild irritation,	III
81-5	Primary Skin Irritation	258738	Non irritant	IV
81-6	Dermal Sensitization	No study	--	--
81-8	Acute Neurotoxicity	42655301	NOAEL = 0.5 mg/kg; LOAEL = 35 mg/kg based on FOB changes	N/A

V. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected and Margins of Exposures for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	MOE
Acute Dietary	NOAEL=0.5 UF = 300	Alterations in Functional Observation Battery Additional 3x for lack of cholinesterase measurement in the critical study	Acute Neurotoxicity-Rat Study	Not Relevant
	Acute RfD =0.002 mg/kg/day			
Chronic Dietary	NOAEL=0.05 UF= 100	Plasma and RBC cholinesterase inhibition (ChEI) in both sexes and brain ChEI in males	1 year dog study	Not Relevant
	Chronic RfD =0.0005 mg/kg/day			
Dietary (Cancer) ^a	Dichlorvos is classified as a Group C Carcinogen.			
Dermal Absorption	11% based on a dermal absorption study			
Short-Term (Dermal) ^a	Maternal (oral) NOAEL =0.1	Cholinergic signs and decreases in body weight	Developmental-Rabbit	300/100 ^b
Intermediate-Term (Dermal) ^a	Oral NOAEL =0.05	Plasma and RBC ChEI at 13 week measurement.	1 year dog study	300/100 ^b
Long-Term (Dermal)	The use pattern dose not indicate long-term exposure potential; therefore, this risk assessment is not required.			
Short-Term (Inhalation) ^a	Maternal (oral) NOAEL =0.1	Cholinergic signs and decreases in body weight	Developmental-Rabbit	300/100 ^b
Intermediate-Term (Inhalation) ^a	Oral NOAEL =0.05	Plasma and RBC ChEI at 13 week measurement.	1 Year -Dog	300/100 ^b
Long-Term (Inhalation)	Inhalation NOAEL= 0.00005 mg/L	Plasma, RBC and brain ChEI	2 year -Rat	300/100 ^b

^a = Oral values were selected, therefore route-to-route extrapolation must be used (11%, dermal absorption factor and 100%inhalation absorption factor).

^b = MOE = 300 for residential exposure (due to the FQPA safety factor) and 100 for occupational exposure risk assessments.